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REVIEW ARTICLE

# The science of dermocosmetics and its role in dermatology

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## Abstract
Our increased knowledge of normal skin physiology has ushered in a subtle revolution in cosmetic science. Originally designed as preparations to enhance personal appearance by direct application on to the skin, cosmetics have now taken on a new role in dermatology, through the support of the management of many skin disorders. This evolving role of cosmetics in skin care is primarily due to scientific and technological advancements that have changed our understanding of normal skin physiology and how cosmetics modify its appearance both physically and biologically. The vast array of techniques currently available to investigate skin responsivity to multiple stimuli has brought about a new era in cosmetic and dermocosmetic development based on a robust understanding of skin physiology and its varied responses to commonly encountered environmental insults. Most cosmetic research is undertaken on reconstructed skin models crucial in dermatological research, given the strict ban imposed by the European Union on animal testing. In addition, the design and conduct of trials evaluating cosmetics now follow rules comparable to those used in the development and evaluation of pharmaceutical products. Cosmetic research should now aim to ensure all trials adhere to strictly reproducible and scientifically sound methodologies. The objective of this review is to provide an overview of the multidisciplinary scientific approach used in formulating dermocosmetics, and to examine the major advances in dermocosmetic development and assessment, the safety and regulatory guidelines governing their production and the exciting future outlook for these dermocosmetic processes following good practice rules.
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## Conflicts of interest
E. Araviiskaia served as a speaker for L'Oreal, La Roche Posay, Vichi, Bioderma, Pierre Fabre, Uriage, Galderma, Glenmark, Merck Sharp and Dohme, Bayer Health Care, Merrz and Stiefel/Glaxo Smith Kline and as a Global Alliance Acne Treatment member, Brimonidine International Global Advisory Board member for Galderma. T. Bieber is advisory panel for L'Oréal. P. Wolkenstein is consultant for L'oreal concerning cosmetic sciences. All the other authors declare no conflict of interest.

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## Introduction
In recent decades, the cosmetic industry has undergone an unobtrusive revolution ushered in by an increasing knowledge of normal skin physiology, as well as the development of new research techniques; consequently, leading to advances in knowledge, and of novel active ingredients and vehicles, based on well-understood mechanisms of action.[1] Together, these scientific and technical advances have also prompted the development of stringent guidelines for the evaluation of cosmetics. Moreover, newly available testing methodologies have increased the understanding of how the physiology of normal and diseased skin, hair and nails is influenced by cosmetics.

Traditionally, cosmetics have been considered preparations, such as powders or creams, designed to enhance personal appearance by direct application on to the skin. However, scientific and technological developments have changed our understanding of the physiology of normal skin and how cosmetics alter its appearance through physical modification and biological activity.[2] Dermocosmetics is now a branch of dermatology using cosmetics in the scientific management of a variety of skin disorders. As skin-care specialists, dermatologists already use dermocosmetics to maintain the aesthetic appearance and feeling of well-being of the skin. Thus, these products alone, or as an adjunct to pharmacological treatment, are regularly used to improve photoprotection, dry or aged skin, inflammatory skin disease such as acne, rosacea, atopic dermatitis, psoriasis and seborrhoeic dermatitis as well as a variety of hair and nail disorders. They are topically applied to the skin, scalp and hair for these reasons, thereby enhancing patients' quality of life (QoL)[3] and self-esteem, and mitigating the adverse effects of some treatments. The development of cosmetics is currently regulated in ways comparable to those of medicinal products; however, the public and dermatologists are generally unaware of this fact. Given that dermocosmetics are now an integral part of the dermatologist's therapeutic arsenal, an understanding of their biological properties and the regulatory environment governing their production and marketing is essential for their safe and effective use. Thus, the aim of this review is to provide an overview of the multidisciplinary scientific approach used to formulate dermocosmetics, to review the major steps of their development and assessment, to outline the safety and regulatory guidelines governing their production and to discuss the outlook for future research and development in the field.

## Development of new techniques in cosmetic research

The vast array of techniques currently available to investigate the skin's response to a variety of stimuli has opened up a new era in the development of cosmetics and dermocosmetics based on a robust understanding of skin physiology, its variations and its responses to commonly encountered environmental insults.[4] It is now clear that the skin is a metabolically and immunologically active organ susceptible to being influenced by externally applied cosmetics and dermocosmetics,[5] and that there is a large variety of skin phenotypes resulting from inherent factors such as ethnicity, genetics, gender and age, as well as external factors such as sun exposure, climate, atmospheric pollution, diet and lifestyle.

Many of the techniques used in the research and development of cosmetics have been developed by the cosmetics industry, with the goal of understanding the normal physiology of skin, hair and nails. Subsequently, many of these have become standard methods used industry-wide to evaluate new products. As an example, the concept of photostable sunscreens was introduced to dermatology by cosmetic research, and worldwide mandatory testing now exists, with established standards for assessing the photostability of UVB and UVA sunscreens, along with their efficacy and safety. In addition, colorimetric methods used to evaluate sunscreens, tanning preparations and whitening products, as well as to measure their irritancy potential,[6] have been adopted as established techniques in cosmetics research.[7]

Nowadays, most cosmetic and dermocosmetic ingredients are tested *in vitro* to measure their precise effect on gene and protein expression. Finished products are assessed through non-invasive *in vivo* techniques (used also for active ingredients in proof-of-concept studies), together with their impact on skin appearance and their feel on the skin. These techniques are extremely useful both for identifying new active ingredients and testing finished products.

### *In vitro* model of reconstructed skin

For the assessment of new ingredients, progressive steps are used, starting with *in silico* techniques (modelization), followed by reconstructed skin models before and moving on to skin explants (*ex vivo*); these stages, where successful, precede further testing of the chosen ingredient(s) after incorporation into a cosmetic formulation through the reconstructed skin models.

Most cosmetic research is now carried out on models of reconstructed skin, which are essential for cosmetic research, given the strict European Union (EU) regulations banning animal testing (excluding pharmaceutical testing). The first *in vitro* model of human skin was the 'living skin equivalent', based on normal human keratinocytes (NHKs) that proliferate and differentiate on de-epidermized dermis.[8,9] Later, the 'living skin' model was replaced by 'reconstructed human epidermis', whereby NHKs were grown on supporting membranes.[10] The EU 2013 ban on animal testing,[11] together with recent advances in tissue engineering, have accelerated the development of a variety of skin disease models based on human skin equivalents,[10] including bacterial skin colonization, cutaneous wounds, autoimmune skin diseases, psoriasis vulgaris, atopic dermatitis, irritant and allergic contact dermatitis, photodamaged skin and melanoma.[10] More recently, tissue engineering has led to the generation of full-thickness skin models (FT models) based on fibroblast-populated collagen matrices (dermal equivalents) overlaid by stratified NHKs.[12] Although originally developed for the treatment of burnt skin and chronic wounds,[13,14] some skin equivalents have now become validated for toxicity testing.[15]

### 'Omics'

Technological advances in cellular and molecular biology now allow researchers to evaluate cutaneous physiological processes at gene, protein and metabolite levels; an exercise sometimes collectively known as 'omics'. Thus, the analysis of gene expression changes at a genome-wide level is known as genomics or 'transcriptomics', system-wide protein analysis as 'proteomics', and the analysis of cellular metabolic processes as 'metabolomics'.[4] Genomics, proteomics and metabolomics, respectively, provide important insights into how skin responds to injury and ageing, as well as the mechanisms by which new interventions and compounds may work to improve its health and integrity.[4] The advent of genomics has enabled researchers to identify how irritant stress, ultraviolet radiation exposure and ageing may affect gene expression in skin cells; as a result, this has led to the identification of markers for the screening of active ingredients, as well as providing indicators of how compounds affect normal skin physiology.[4,16]

## Non-invasive *in vivo* techniques

The emergence of high-throughput technologies, such as microarrays, along with significant improvements in analytical chemistry, mass spectroscopy and nuclear magnetic resonance, have revolutionized analysis of the skin's response to the environment.[4] New microscopy tools and imaging techniques also provide non-invasive, real-time 'virtual biopsies' of skin models.[17,18] The use of ultrasound technology to visualize skin *in vivo* was the predecessor of more advanced imaging tools (such as confocal microscopy, magnetic resonance imaging, Raman microscopy) used to monitor skin biomolecular changes in real time, and thus assess the effectiveness of cosmetics on skin hydration and anti-ageing,[17] and two-photon microscopy.[19] New ultrasonic imaging techniques have revealed a subepidermal non-echogenic band at the level of the papillary dermis, the thickening of which is a marker of both ageing and photoageing.[20] Together, these technological advances have elevated the development of cosmetics and dermocosmetics to a highly scientific level.

## Development of cosmetic formulations

The main objective in the development of a cosmetic formulation, from solid pastes to emulsions and aqueous lotions, is to ensure the bioavailability of its active ingredients, along with their stability, microbiological cleanliness, safety, and comfortable feel on the skin of the user.[11,21] In brief, the product should meet and maintain the required physical, chemical and microbiological quality standards, as well as the desired functionality and aesthetics, when stored under appropriate conditions.[22] The identification of an ideal vehicle for the skin delivery and bioavailability of its contained active ingredients is critical to achieving the appropriate equilibrium between these ingredients and the skin.[23,24] Therefore, the final formulation of a cosmetic should ensure the long-term stability (up to 3 years) of the active ingredients, in that associated inactive compounds may have a profound impact on the fate of the active ones.[25] In addition, the feel on the skin of a cosmetic strongly affects any user's liking for it and therefore whether it will be used; thereby having a direct impact on user adherence.[26]

In a systematic literature review, patient adherence to the use of topical treatment for psoriasis in randomized controlled trials was 55–100%, the most frequently cited reasons for non-adherence being low treatment efficacy, lack of time to apply it, fear of the active ingredient, for example steroids, and its poor cosmetic acceptability.[27] In a study, assessing adherence to acne treatment, the use of cosmetics such as moisturizers and cleansers was associated with better adherence[28]; therefore, the aim of including testing of the feel of a cosmetic on the skin is to achieve the most satisfactory formulation to satisfy the user and thereby deliver its active contents into the skin.[25]

The choice of ingredients is from amongst molecules that have been tested as safe, and belong to a 'positive list' of ingredients with agreed types, dosages, application sites and methods of usage.[11,29] In addition, users are provided in the package insert with information on all the safety assessments used in a product's development as well as on its composition and potential adverse effects.[11]

Cosmetic formulations are tailored to user age, skin phenotype and occupation, body region for application, season of year, and local climate conditions. The number and nature of the active ingredients in a particular formulation varies also according to their targeted users and uses, for example children, sensitive skin and normal skin. Sensitive skin is a condition characterized by high subjective skin sensitivity, which may present with or without other clinical symptoms, appear alone or in association with other skin disorders such as seborrhoeic dermatitis, and have considerable impact on patient QoL.[30] All new ingredients, whether of natural or synthetic origin, undergo a skin sensitization risk assessment to provide a quantitative risk value for a particular product type.[31] Moreover, in recent years, dermatologists have raised increasing concerns about allergic contact dermatitis to cosmetics, which can be induced particularly by some fragrances, but also by many other possible ingredients. As a consequence, some dermocosmetics do not contain any fragrances or may have their number of ingredients restricted as far as possible. Accordingly, the European Scientific Committee on Cosmetic Products and Non-Food Products (SCCPNFP) have issued a guidance document containing a list of forbidden fragrance ingredients.[32] In addition, an international task force has been set up by the European Cosmetics and Personal care Association (Cosmetics Europe), in conjunction with major cosmetic groups, to develop routine *in vitro* testing methodologies to assess the allergic potential of new ingredients.[33]

Cosmetics research also focuses on developing new testing procedures to evaluate the impact of products and ingredients on the environment. Examples of such impact include a product's water use, the biodegradability of its ingredients, the nature of its packaging and its carbon footprint, which should comply with the International Registration, Evaluation, Authorisation and Restriction of Chemical (REACH) substances programme.[34] In addition, new ways of packaging are constantly being developed to prevent product contamination or oxidation; thereby diminishing the potential for ingredients, preservatives or stabilizers to injure or sensitize.

 

**Table 1** Examples of some techniques developed to assess the safety and efficacy of cosmetics and dermocosmetics

| Investigating techniques | Parameter(s) recorded | Cosmetic/dermocosmetic applications | Dermatological/medical applications |
|---|---|---|---|
| Surface analysis | | | |
| Optical (photos, visioscan, chromasphere, fringe projection, Image analysis, replicas, densiscore, mexameter, colorimeter, erythometer. . .) | Colour, dyschromia, individual typology angle, microrelief, deep and fine lines, pore size, microcirculation | Whitening, anti-wrinkles (skin ageing), typology, dark spots, determination of minimal erythema dose, SPF, incident polarization angles/sunscreen testing (UVB and UVA)[64–66] | Melasma, vitiligo, polymorphic light eruption lentigines/UV/ photoaging acne, minimal erythema dose/phototyping/ individual typology angle, contact dermatitis[76–78] |
| Biometric (transepidermal water loss, sebumeter, sebutape, corneometer, skinchip, scrub, dsquame. . .) | Water loss/barrier function, sebum level, hydration, omics (microflora, proteomic. . .) | Hydration, dry skin, oily skin, desquamation, hygiene, stratum corneum functions[67,68] | Acne, xerosis, ichthyosis, peelings, atopy[79–81] |
| Structural (echography A and B, NMR and fluorine NMR) | Tissue thickness (epiderm, dermis, hypodermis), atrophy, acanthosis | Tissue turnover, exfoliative process (keratolytics), sunburn (oedema), skin ageing, sensitive skin, cellulitis[69–71] | Steroid therapy, psoriasis, contact dermatitis, anti-inflammatory[82–84] |
| Physical properties (torquemeter, cutometer, indentometer) | Elasticity epidermis and dermis, firmness, recovery | Hydration, epidermal and dermal anti-ageing, photo-aging[72–74] | Dermal diseases, steroid therapy[85–87] |
| Microcirculation (Doppler, photoplethysmography, thermography) | Erythema, MED, sunscreen testing, soothing | Soothing products, anti-irritant[75] | Local hypoxia, inflammatory disorders[88,89] |
| Ultrastructural techniques | | | |
| Non-invasive: NMR imaging, confocal microscopy, multi-photon microscopy | Tissues structures, thickness of stratum corneum, epidermis, dermis (papillary/reticular). Cellular and molecular organization, melanization. . .in real time | Research models for melanization and dermal processes such as collagen renewal or organization (whitening, anti-ageing)[90–92] | Can apply to all skin diseases. Real-time non-invasive ‘biopsies’, malignant processes[93–95] |
| Invasive (punch biopsy): histological and immunohistological. Electronic microscopy (scanning, transmission) Biochemical | Detailed structures and functions (immunomarkers) Sunburn cells. . . Genomic, proteomic. . . | UV protection (sunburn cells, Langerhans cells. . .) | As above |
| Psychological and physiological scorings | | | |
| Self-assessed controlled questionnaires (Beauty QoL, WHO QOL26, DLQI, OSSIQ. . .) Cosmeticity questionnaire | QoL, self-esteem, social relations. . . As defined by the WHO, mental balance is an integrated part of human health | Impact of products or processes (hairdressing, make up) upon daily life/psychological compartment[38,39] | QoL and skin diseases. How the use of dermocosmetics can mentally help seriously ill or disfigured patients[96–102] |

The explored parameter(s), fields of applications and their extensions to dermatological or medical concerns. Their classification, in this table, is primarily and arbitrarily based on technique definition. Since most techniques are versatile, many can apply to different objectives.
DLQI, Dermatology Life Quality Index; NMR, nuclear magnetic resonance; OSSIQ, Oily Skin Self-Image Questionnaire; QOL, Quality of Life; SC, subcutaneous; SPF, sun protection factor; UV, ultraviolet; WHO, World Health Organization; WHO QOL26, World Health Organization Quality of Life-26 item.

## Developments in the evaluation of cosmetic formulations

Over the last four decades, cosmetic research has made huge efforts to develop non-invasive techniques to evaluate the *in vivo* effects of finished products. Some examples of such techniques are summarized in Table 1, in which it can be seen that most are versatile, such that they have become essential tools for dermocosmetic research.

In 2008, Cosmetics Europe issued guidelines standardizing the evaluation of cosmetic product efficacy, which delineated the general principles for designing cosmetic clinical trials, established the basic information required for all study protocols and provided an overview of validated methodologies.[35] These testing methodologies were selected because they had been validated in both academic research and the cosmetics industry, including some by the European Group on Efficacy Measurements of Cosmetics and Other Topical Products (EEMCO). Cosmetics Europe guidelines overall recommend that the evaluation of cosmetics should combine instrumental measurements from both *in vivo* and *in vitro* model systems under controlled conditions.

More recently, standardization has been assisted by the development of skin atlases to assess the facial clinical signs of subjects of different ethnicities, with any age-induced skin changes being scored by means of standardized photographs.[36] Such

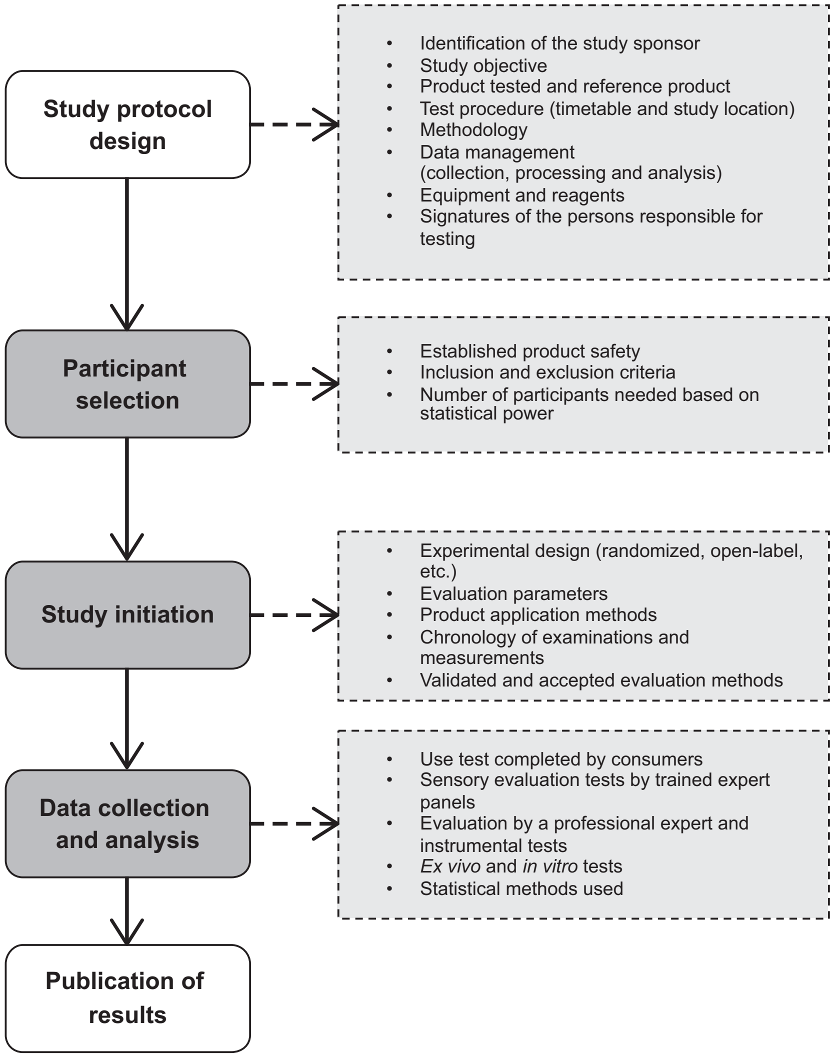


**Figure 1** Schematic diagram of standard testing protocols for cosmetics and the information required at each stage of the study.*

*Adapted from Cosmetics Europe.[35]

atlases appear promising in that they offer clinical standards for facial attributes and standardized guidance for clinical assessments.

As described in Table 1, major tests used to assess the benefit and safety of cosmetics and dermocosmetics include surface analysis by direct or standardized photography, biometrical methods, histological, ultrastructural and biochemical analysis and questionnaires on QoL and the cosmetic acceptability of products. Skin feel testing should be conducted by expert panels or by user assessment, so as to evaluate user well-being, psychological impact and QoL.[35]

Skin sensation properties are a very important feature of cosmetics; a user's appreciation of a cosmetic may lead to its immediate rejection or to long-term product loyalty. Thus, skin feel analyses are systematically performed during cosmetic product development.[37] The feel of a product, coupled with a product's biological properties are able to impact highly on user QoL and well-being, thereby affecting their self-esteem.[38] The psychological impact of skin disorders on QoL may be assessed through the use of validated tools, namely the BeautyQoL,[39] the World Health Organization Quality of Life-26 item (WHOQOL-26) Questionnaire, the Dermatology Life Quality Index (DLQI),[40] and the Oily Skin Self-Image Questionnaire (OSSIQ).[41]

Current guidelines recommend that the design and execution of trials evaluating cosmetics should follow rules comparable to those used in the development and evaluation of pharmaceutical products[42] and abide by the Consolidated Standards of Reporting Trials (CONSORT) guidelines[43] (Fig. 1). Evaluating the efficacy of cosmetic products must include reliable and reproducible methods following well-designed and scientifically validated methodologies in accordance with good clinical research practice; consequently,[44] a brief description of the tools used (including to assess QoL, and skin sensation analysis) and the clinical outcomes to be assessed should all be documented. Moreover, studies on human volunteers should follow all ethical rules associated with the testing of products on human subjects along with the same strict inclusion and exclusion criteria. Data recording, transformations and representations in tabular or graphical form should all be transparent and clearly explained, and all data analyzed by appropriate statistical analysis.[35]

The use of well-designed and scientifically validated methodologies for the clinical testing of cosmetic products can transform the therapeutic arsenal that dermatologists have at their disposal. Thus, randomized, double-blind, vehicle-controlled studies of cosmetics provide reliably validated evidence of the value of a given cosmetic product towards producing the required dermatological outcome.[45–47]

Furthermore, with regard to the advertising of cosmetic products, this issue is addressed by the European Commission Regulation 655/2013, and in 2012 Cosmetics Europe launched a self-regulatory charter setting out the cosmetics industry's common ground on responsible cosmetic advertising and marketing in Europe.[48]

## Developments in the safety surveillance of cosmetic formulations

All safety assessments (pre-launch) and post-marketing surveillance (post-launch) for a given cosmetic formulation are carried out by the manufacturers, which is a similar process to medical products and devices. EU standards now call for manufacturers as well as cosmetic importers to retain full information on a product in a Product Information File for 10 years from the date the last product batch entered the market.[11,49] This document should include its composition, its safety assessment data, the manufacturing process used and any possible undesirable effects.

Post-marketing surveillance of cosmetic products entails the monitoring by companies and competent authorities of the safety of products on the market. Current directives in the EU[29] provide guidelines for the cosmetic industry on receiving, handling, evaluating, classifying and reporting undesirable events associated with the use of cosmetic products.[35] As a result in 2013, the Platform of European Market Surveillance Authorities for Cosmetics (PEMSAC) was established to facilitate cooperation and coordinate all activities in the field of cosmetics market surveillance.[50]

## Future prospects

Cosmetics and dermocosmetics have steadily progressed from instruments of adornment to scientifically designed treatments for the appearance and feel of the skin, as advances in science and technology have expanded the tools available to design, develop and test bespoke products for target audiences according to age, ethnic background, lifestyle habits and type of skin.

The skin's microflora protect the body from invasion by more pathogenic organisms, and it might be possible to not only destroy bad bacteria but actively add good bacteria to skin creams in order to fight skin conditions such as acne.[51] It is this balance and role of endogenous skin microflora that will be key for new cosmetic or dermatological applications.

Epidermal barrier dysfunction is an important factor in the pathogenesis of inflammatory skin disease.[52] Research has demonstrated the effect of cosmetics on the physiological parameters of the skin barrier, in that moisturizers for example have been shown to significantly improve skin conditions and QoL for psoriasis patients.[53,54] Furthermore, moisturizers containing humectants have consistently led to statistically significant improvements in skin dryness,[55] while in patients with atopic dermatitis, the routine use of topical physiological lipid emollients can delay the need for topical glucocorticoid therapy.[56] In addition, the use of cosmetics including moisturizers and cleansers are associated with improved adherence to acne therapy.[28]

The use of dermocosmetics for a variety of skin disorders may be expanded into areas not necessarily considered the brief of dermatologists, such as the management of cutaneous side-effects associated with targeted oncotherapy:[57–61] epidermal growth factor receptor inhibitors and other monoclonal antibodies.[62]

Thus, an algorithm has been developed for the appropriate use of dermocosmetics in the management of these side-effects.

Skin feel testing of cosmetics is of paramount importance in ensuring their acceptance by the user. Of note in this respect is the 'exposome', a new concept in such assessment taking account of the user's environment, to include his or her social activities, lifestyle habits, and food and alcohol consumption, as well as any physiological or psychological aspects that may be associated with his or her skin or other disease, pharmaceutical treatment or cosmetic use.[63]

Evidence gathered in recent decades has significantly improved our understanding of normal and pathological skin biology. Moreover, we now understand much better how skin-care products modulate skin quality and function. New research has clearly demonstrated that even seemingly normal skin may be affected by changes identified in gene transcription activity as the skin responds to an ever-changing environment of temperature, humidity, pollution, physical and chemical stressors, such as ultraviolet radiation exposure or even cleansing. The application of novel research technologies will continue to expand our understanding and change how we approach skin care.[4] The standards for testing cosmetic products will also continue to evolve; as it is vital that trials designed to test cosmetic and dermocosmetic efficacy and safety continue to adhere to strict methodologies that are reproducible, scientifically sound and in accordance with the latest approved guidelines.[43]

## Conclusions

Recent advances in technology, together with an increased knowledge of skin physiology, have propelled cosmetics into a new era of scientifically designed products for the treatment and management of a wide range of skin phenotypes and disorders. The vast array of scientific and technological advances supporting this development has also led to new and strict guidelines for the development and testing of cosmetics, comparable to those used for pharmaceutical products. This scientific and technological revolution has given rise to modern cosmetics and has also made them a major part of the dermatologist's therapeutic armamentarium. In future, it is clear that they will become steadily more important and eventually indispensable by increasing drug efficacy and decreasing their adverse effects, while also improving patient QoL and psychological mood.

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